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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 09/902,713

Filing Date: July 10, 2001

Appellant(s): GODDARD ET AL.

Christopher De Vry
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 20 May 2008 (with supplemental appeal briefs filed 02 July 2008 and 23 September 2008) appealing from the Office

action mailed 30 November 2007. The appeal brief submitted 20 May 2008 contains the bulk of the brief, including all of the arguments and the evidence appendix. The supplemental appeal brief submitted 02 July 2008 provides a corrected summary of the claimed subject matter. The supplemental appeal brief submitted 23 September 2008 provides the claims appendix which was missing from the original appeal brief.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the Appeal Brief of 20 May 2008.

(2) Related Appeals and Interferences

The Appellant has correctly identified the related appeals, interferences, and judicial proceedings in the Appeal Brief of 20 May 2008. Also, the Board is advised that there are numerous applications filed by Genentech relying upon the gene amplification assay for utility which are under nearly identical rejections and/or appeals. Appellants are in the best position to identify these other applications for the Board.

(3) Status of Claims

The statement of the status of claims contained in the Appeal Brief of 20 May 2008 is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the Appeal Brief of 20 May 2008 is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the supplemental Appeal Brief received 02 July 2008 is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal appearing in the Appeal Brief of 20 May 2008 is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the Supplemental Appeal Brief received 23 September 2008 is correct.

(8) Evidence Relied Upon

Pennica, D. et al. "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors" Proc. Natl. Acad. Sci., vol95 (December 1998, pp. 14717-14722.
Konopka, J.B. et al. "Variable expression of the translocated c-abl oncogene in Philadelphia-chromosome-positive B-lymphoid cell lines from chronic myelogenous leukemia patients" Proc. Natl. Acad. Sci. USA, vol83 (June 1986), pp. 4049-4052.

Godbout, R. et al. "Overexpression of a DEAD box protein (DDX1) in neuroblastoma and retinoblastoma cell lines" J. Biol. Chem. vol273, no. 33 (14 August 1998), pp. 21161-21168.

Li, R. et al. "Identification of putative oncogenes in lung adenocarcinoma by a comprehensive functional genomic approach" Oncogene vol25 (2006), pp. 2628-2635.

Sen "Aneuploidy and cancer" Curr. Opin. Oncol. vol12 (2000), pp. 82-88.

Hanna, J.S. and Mornin, D. "HER-2/neu Breast Cancer Predictive Testing" Pathology Associates Medical Laboratories (1999), pp. 1-2.

Hittelman, W. "Genetic Instability in Epithelial Tissues at Risk for Cancer" Ann. NY Acad. Sci. vol952 (2001), pp. 1-12.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-43 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

Claim 39 is directed to an isolated antibody that specifically binds to the polypeptide of SEQ ID NO: 96. Dependent claims 40-43 are directed to various forms of an antibody according to claim 39; specifically, monoclonal, humanized, fragment and labeled forms. Whether or not the claimed antibodies have utility and are enabled depends entirely on whether or not the polypeptide they bind has utility and is enabled. The specification discloses the polypeptide of SEQ ID NO: 96, also known as PRO269. Appellants have gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides. See Appeal Brief (received 20 May 2008), p. 4, third paragraph.

At pages 222-235 of the specification, Example 92 discloses a gene amplification assay in which genomic DNA encoding PRO269 had a ΔCt value of at least 1.0 for eight out of seventeen lung tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. Example 92 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 222, lines 28-30).

First, there are several problems with the data provided in this example. PRO269 was reported as being amplified in less than half of the lung tumor samples tested. Therefore, if a new tumor lung sample were tested for PRO269 amplification, it is more likely than not that the PRO269 diagnostic test would yield a false negative result.

Second, the art recognizes that lung epithelium can be aneuploid without the presence of cancer, and that aneuploidy at the genomic DNA level cannot be presumed to correlate with overexpression at the mRNA or protein levels. Specifically, Hittelman (2001, Ann. N.Y. Acad. Sci. 952: 1-12) reports that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy **before** the epithelial cells turn cancerous. See especially p. 4, Figure 4. Also, Sen (2000, Curr. Opin. Oncol. 12:82-88) teaches that cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes. Thus, Sen teaches that a slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The gene amplification assay in the instant specification does not provide a comparison between the lung tumor samples and normal lung epithelium and does not correct for aneuploidy. Thus it is not clear that PRO269 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium. One skilled in the art would not conclude that PRO269 is a diagnostic probe for lung cancer unless it is clear that PRO269 is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium.

Third, even if the data had been corrected for aneuploidy and a proper control had been used, the data have no bearing on the utility of the claimed PRO269 *antibodies* or the polypeptide they bind. In order for PRO269 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO269

mRNA or PRO269 polypeptide levels in lung tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels. A specific example of the lack of correlation between genomic DNA amplification and increased mRNA expression is provided by Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

"An analysis of *WISP-1* gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP-3* RNA was seen in the absence of DNA amplification. In contrast, *WISP-2* DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." Another specific example is provided by Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the *abl* gene but to variation in the level of *bcr-abl* mRNA produced from a single *Ph1* template" (see abstract). Hanna and Mornin (1999, Pathology Associates Medical Laboratories) provide another important example of a lack of correlation between gene amplification and mRNA/polypeptide overexpression, wherein diagnosis of breast cancer included testing both the amplification of the *HER-2/neu* gene as well as over-expression of the *HER-2/neu* gene product. Thus Hanna and Mornin constitute evidence that those of skill in the art realize that the level of polypeptide expression must be tested empirically to determine whether or not the polypeptide can be used as a diagnostic marker for a cancer. The

specification does not provide data as to whether or not the polypeptide level of PRO269 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed antibodies is not in currently available form, and further experimentation is required to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

The general concept of gene amplification's lack of correlation with mRNA/polypeptide overexpression in cancer tissue is addressed by Godbout et al. (1998, J. Biol. Chem. 273(33):21161-8), who teach a general lack of correlation between gene amplification and mRNA/polypeptide overexpression. The abstract of Godbout et al. teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified.***" (emphasis added). The polypeptide encoded by the DDX gene had been characterized as being a putative RNA helicase, a type of enzyme that would be expected to confer a selective advantage to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state "***It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both

genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO269 confers any growth advantage to a cell, and thus it cannot be presumed that the PRO269 polypeptide is overexpressed because the genomic DNA including the gene being studied is amplified.

An additional reference that provides evidence that gene amplification does not generally lead to increased transcript is Li et al. (2006, Oncogene, Vol. 25, pages 2628-2635). Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "***In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels,*** implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma.*" Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that gene amplification does NOT correlate with increased protein levels,*** absent

evidence that the polypeptide has biological relevance in cancer. There is no such evidence for PRO269.

Therefore, data pertaining to PRO269 genomic DNA do not indicate anything significant regarding PRO269 polypeptides or the claimed antibodies that bind them. The data do not support the specification's assertion that PRO269 polypeptides or antibodies can be used as cancer diagnostic agents or cancer therapeutic targets. Significant further research would have been required of the skilled artisan to reasonably confirm that the PRO269 polypeptide is overexpressed in any cancer to the extent that the polypeptide or antibodies could be used as cancer diagnostic agents, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO269 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO269 **antibodies as** diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides and antibodies. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the preponderance of the totality of the evidence supporting the

rejection (Pennica et al., Konopka et al., Sen, Hittelman, Godbout et al., Li et al., and Hanna and Mornin), the rejection is properly maintained.

Claims 39-43 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(10) Response to Argument

All of Appellants' arguments are contained within the Appeal Brief received 20 May 2008. Therefore, when referring the "the Brief" in this section of the answer, the examiner is referring solely to the Appeal Brief of 20 May 2008.

At p. 4 of the Brief, Appellants briefly review the gene amplification data disclosed in the specification, and refer to the Goddard declaration submitted under 37 C.F.R. 1.132 on 31 March 2003 as supporting the assertion that the gene is a useful marker for diagnosis of lung cancer. This has been fully considered but is not found to be persuasive as it is off-point. Specifically, the claims are directed to PRO269 antibodies, not PRO269 genes.

At pp. 4-5 of the Brief, Appellants argue that ample evidence has been submitted to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded polypeptide is expressed at an elevated level. Appellants briefly point to Orntoft et al., Hyman et al., and Pollack et al. Finally, Appellants assert that even if a

polypeptide encoded by an amplified gene were not overexpressed, it would still have a specific, substantial and credible utility as tools for more accurate tumor classification.

Appellants briefly point to the Ashkenazi declaration submitted under 37 C.F.R. § 1.132 and the Hanna and Mornin reference as supporting their position. This has been fully considered but is not found to be persuasive. Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract). It would appear that Appellants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded polypeptide. Hyman et al. found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO269 would be correlated with elevated levels of mRNA, much less polypeptide. Hyman et al. do not examine polypeptide expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung cancer. Finally, the Ashkenazi declaration and the Hanna and Mornin reference support the Examiner's position in that

they provide further evidence that gene amplification does not correlate with increased mRNA/polypeptide levels. It is noted that nowhere in the specification is it asserted that tumors could be more accurately classified if the genomic DNA is amplified and the polypeptide is not overexpressed.

At p. 5, second paragraph, of the Brief, Appellants argues that the sale of gene expression chips constitutes evidence that the research community believes that the information obtained from these chips is useful in that it is more likely than not that the information is informative of polypeptide levels. This has been fully considered but is not found to be persuasive for two reasons. First, evidence of commercial success, while probative as a secondary consideration of non-obviousness, has no bearing on the legal issue of utility and enablement. Second, gene chips speak to the issue of whether mRNA levels are predictive of polypeptide levels, which is no longer relevant to the instant rejections.

At p. 5, third to fifth paragraphs, Appellants conclude that the evidence supports that gene amplification correlates with increased mRNA expression. Appellants urge that the skilled artisan would have found it credible that the claimed PRO269 antibodies would have utility for the diagnosis of tumors, monitoring cancer development, and/or measuring efficacy of cancer therapy. Appellants further assert that the claimed antibodies are enabled. This has been fully considered but is not found to be persuasive. As discussed above, the examiner believes that the preponderance of the totality of the evidence indicates that gene amplification is not generally associated with increased mRNA expression, especially in lung epithelium. See Pennica et al.,

Konopka et al., Hittelman, Sen, Godbout et al., Li et al., and Hanna and Mornin. Furthermore, it is noted that the utility rejection is *not* based on whether or not the asserted utility is *credible*. Rather, the rejection is based on the position that the asserted utility is not *substantial*. The prior art indicates that gene amplification cannot be presumed to correlate with increased mRNA and polypeptide production, and thus the polypeptide levels must be independently measured. See Hanna and Mornin, Godbout et al., and Li et al. Since the utility is not in currently available form, and the claimed material *must* be further tested in order to determine whether or not it is useful as per the asserted utility, the utility is not substantial.

Appellants' detailed arguments begin at p. 6 of the Brief. Appellants begin with a review of the legal standard for utility, with which the examiner takes no issue.

Beginning at p. 9 of the Brief, Appellants review Example 92, and refer to the Goddard declaration as establishing that an amplification of at least 2-fold is significant and indicative of a cancer diagnostic marker. The Goddard declaration under 37 CFR 1.132 filed 31 March 2003 is insufficient to overcome the rejection of claims 39-43 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996).

Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2 fold to 3.5 fold amplification in eight out of seventeen lung tumor samples is significant, and whether such data have any relevance to the claimed subject matter, i.e., antibodies that specifically bind PRO269 polypeptides. The significance can be questioned based on the strength of opposing evidence. In the instant case, the controls used were not matched, non-tumor lung samples but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al., Konopka et al.). This art, as well as the Hittelman, Sen, Godbout et al., and Li et al. references cited above, constitute strong opposing evidence as to whether or not the claimed antibodies have utility and enablement based on a presumption of polypeptide overexpression in view of gene amplification data. Finally, while the Goddard declaration speaks to the utility and enablement of genes, it does not speak to whether or not the encoded polypeptides are also found at increased levels in cancerous tissues. Since the claims under examination are directed to polypeptides, not genes, this question is critical.

At p. 11 of the Brief, Appellants argue that their gene amplification was not due to aneuploidy. Appellants refer to the Ashkenazi declaration as showing that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Appellants agree with Sen and Hittelman that aneuploidy can be a feature of damaged tissue and may not invariably lead to cancer. However, Appellants urge that Sen and Hittelman support their position that

PRO269 is still useful in diagnosing pre-cancerous lesions or cancer itself. Appellants argue that the art published around the filing date of this application suggested that identification of pre-cancerous lesions were important in preventive diagnosis, Appellants take the position that, based on the well-known art, there is utility in identifying genetic markers in epithelial tissues at cancer risk. This has been fully considered but is not found to be persuasive. First, there is no evidence that the data in the specification were not due to aneuploidy, since no controls for aneuploidy were used. Also, Appellants' argument and the declaration of Dr. Ashkenazi (received 16 October 2003) contradicts the assertion of utility in the specification. Specifically, at p. 222 the specification states:

"Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers and diagnostic determination of the presence of those cancers. Therapeutic agents may take the form of antagonists of the PRO polypeptide, for example, murine-human chimeric, humanized or human antibodies against a PRO polypeptide."

It is clear from this passage that the specification does not assert a utility for the claimed antibodies in diagnosing *damaged* tissue or *pre-cancerous* lesions, or identifying epithelial tissues *at cancer risk*. Therefore, Appellants' argument and the Ashkenazi declaration are inconsistent with the assertion of utility made in the specification.

Beginning at p. 11 of the Brief, Appellants criticize Pennica et al. and Konopka et al. as not being specific to PRO269, instead as being specific to other genes, and not establishing a general trend. Appellants urge that there is no legal requirement for accurate prediction, and that it is more likely than not that gene amplification correlates

with polypeptide overexpression. This has been fully considered but is not found to be persuasive. The instant application also presents data from a single gene at a time and makes conclusions about gene products from genomic DNA data. Pennica et al. and Konopka et al. constitute evidence that it cannot be assumed that amplified genomic DNA results in overexpressed gene product. Godbout et al. and Li et al. also provide evidence to this effect with respect to the general concept of whether or not gene amplification correlates with increased mRNA/polypeptide expression. Finally, Hittelman and Sen constitutes evidence that, in general, non-cancerous epithelial tissues are frequently aneuploid, and thus an increase in genomic DNA is not diagnostic of cancer.

Beginning at p. 13, Appellants discuss the Godbout et al. and Li et al. references. Appellants urge that Godbout et al. was cited as evidence that gene amplification correlates well with polypeptide expression levels. Appellants argue that they never asserted that PRO269 was similar in any way to the DDX1 gene of Godbout et al., that selective advantage to cell survival is not the only mechanism by which genes impact cancer, and that structure/function data is not required for utility. This has been fully considered but is not found to be persuasive. Godbout et al. make a strong case in favor of the rejection. Specifically, Godbout et al. state, "*It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell.*" There is no evidence or assertion of record that PRO269 provides a selective growth advantage to a cell, and thus it cannot be presumed that the polypeptide is overexpressed because the genomic DNA including the gene being

studied is amplified. PRO269 is not a putative oncogene, and the function of the encoded polypeptide is not known. Godbout et al. clearly point out that whether or not a polypeptide is over-expressed depends strictly upon the function of the polypeptide. The instant specification has not established that over-expression of PRO269 polypeptide provides a growth advantage to a cell, and thus it cannot be said that Godbout et al. constitute evidence to support Appellants' position. In fact, Godbout et al. support the instant rejection. Finally, there is no guidance in the specification or prior art regarding what mechanism other than selective advantage to cell survival contributes to cancer development.

At p. 14, Appellants take issue with Li et al. Appellants urge that Li et al. acknowledge that their results differed from those of Hyman et al. and Pollack et al., and note that the difference may be due to different methodologies. Appellants refer to the supplemental information accompanying the Li et al. article. Appellants urge that Li et al. used an amplification copy ratio of only 1.4, which is not significant according to the Goddard declaration, and that a copy number of at least 2 was necessary. This has been fully considered but is not found to be persuasive. First, it is noted that Hyman et al. also found that less than half of the amplified genes were overexpressed at the mRNA level, even though they only investigated genes in genomic DNA regions that were amplified at least 2-fold (argued in more detail above). Furthermore, Li et al. did not limit their studies to genes that were amplified at less than 2-fold. In fact, the supplemental information indicates that some of the samples were required to bind with a probe requiring at least 2-fold amplification:

Genes with copy number ratio > 1.40 (representing the upper 5% of the CGH ratios across all experiments) were considered to be overrepresented. A genomic fragment that contained six or more adjacent probes showing a copy number ratio > 1.40, or a region with at least three adjacent probes with a copy number ratio > 1.40 and no less than one probe with a ratio > 2.0, were considered to be amplicons. (emphasis added, from 1st page of supplemental material)

Beginning at p. 14 of the Brief, Appellants argue that it is more likely than not that amplified genes have increased mRNA. Appellants point to Example 92 of the specification as disclosing that amplification is associated with overexpression of the gene product, indicating that the polypeptides and their antibodies are useful targets for therapeutic intervention and diagnostic determination. This has been fully considered but is not found to be persuasive. Several pieces of evidence contradict this statement by showing that gene amplification cannot be assumed to correlate with gene product overexpression. See Pennica et al., Konopka et al., Hittelman, Sen, Godbout et al., Hanna and Mornin, and the Ashkenazi declaration, all of record.

At pp. 14-16 of the Appeal Brief, Appellants refer to Orntoft et al., Hyman et al., and Pollack et al. as evidencing that, in general, gene amplification increases mRNA expression. This has been fully considered but is not found to be persuasive. Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract). It would appear that Appellants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded polypeptide. Hyman et al. found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high

amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO269 would be correlated with elevated levels of mRNA, much less polypeptide. Since Hyman et al. found that less than half of the amplified genes were overexpressed at the mRNA level, Hyman et al. supports the basis of the rejections that it is more likely than not that gene amplification *fails* to correlate with increased mRNA/polypeptide levels. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung cancer. Interestingly, Pollack et al. add a cautionary note in their discussion section that there may be differences in correlations depending on what tissue is being studied. Specifically, at p. 12967, Pollack et al. refer to Platzner et al., who find a poor correlation between DNA amplification and overexpression. Pollack et al. discuss how this difference may be due to different methodology, but also may be due to real biological differences between breast and colon tumors (p. 12968). It is noted that PRO269 is reported in the specification as being amplified in lung carcinomas, whereas Pollack et al. studied breast cancers. Li et al. studied lung carcinomas, and found poor correlation. Li et al. include a similar cautionary note that their results may be tissue-dependent (p. 2629). Therefore, Li et al. is the more relevant piece of evidence, in that it concerns the same type of cancer for which the specification

asserts PRO269 is a marker. Also interesting is that Pollack et al. used a normal female leukocyte DNA control from a single donor rather than normal breast tissue (matched tissue control), whereas Platzer et al. compared colon cancer samples to normal colon epithelium, and Li et al. compared lung carcinoma samples with normal lung tissue.

At p. 16, third paragraph, of the Brief, Appellants argues that the sale of gene expression chips constitutes evidence that the research community believes that the information obtained from these chips is useful in that it is more likely than not that the information is informative of polypeptide levels. This has been fully considered but is not found to be persuasive for two reasons. First, evidence of commercial success, while probative as a secondary consideration of non-obviousness, has no bearing on the legal issue of utility and enablement. Second, gene chips speak to the issue of whether mRNA levels are predictive of polypeptide levels, which is no longer relevant to the instant rejections.

At the fourth paragraph of p. 16 of the Brief, Appellants argue that the examiner appears to disregard the evidence of the articles relied upon by Appellants based on misinterpretations of their teachings. Appellants argue that the articles lend support that an amplified gene is more likely than not also overexpressed. Appellants urge that this interpretation would be viewed as reasonable and credible by the skilled artisan. Appellants argue that the "more likely than not" standard is a much lower standard than a "necessary" or "accurate" correlation. Appellants assert that the examiner has not cited any evidence or advanced any arguments as to why Appellants' statement of

overexpression of polypeptide would not be credible. This has been fully considered but is not found to be persuasive. Patentable utility must be credible, specific, and substantial. Credibility and specificity have not been questioned. However, the asserted utility is not substantial because it would require further research to reasonably confirm a real world use. The rejection is supported by several pieces of evidence that show that gene amplification cannot be assumed to correlate with polypeptide overexpression. See Pennica et al., Konopka et al., Sen, Hittelman, Godbout et al., Li et al., Hanna and Mornin, and the Ashkenazi declaration. Since the priority filing date of October 1997, no evidence has been brought forth on the record as to whether or not the polypeptide level of PRO269 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed antibodies that bind polypeptides is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

At pp. 16-17 of the Brief, Appellants argue that Hyman et al. reported a clinical association between HOXB7 amplification and poor patient prognosis, thus suggesting that the research was relevant to identifying probes that can be used as cancer diagnostics. Appellants also point to Pollack et al.'s final paragraph as implying a diagnostic utility. This has been fully considered but is not found to be persuasive. Hyman et al. and Pollack et al. relied on significant further research to identify a very small number of genes that had potential as cancer markers. For example, Hyman et al. identified 270 specific amplified genes, but only identified one, HOXB7, as being

potentially associated with poor prognosis. Hyman et al. only suggested such in view of other research that had already linked HOXB7 to cancer. See second paragraph on p. 6244, wherein Hyman et al. refer to six other research papers regarding HOXB7 and cancer, including experiments wherein HOXB7 was transfected into normal cells and induced cell proliferation and tumorigenicity. Pollack et al.'s final paragraph contains several cautionary notes about their findings, including a specific statement at p. 12968 that "this finding cautions that elevated expression of an amplified gene cannot alone be considered strong independent evidence of a candidate oncogene's role in tumorigenesis....This highlights the importance of high-resolution mapping of amplicon boundaries and shape..on a large number of samples, in addition to functional studies." Thus, the art clearly directs the skilled artisan to further experimentation before identifying any amplified gene or its expression product as a diagnostic marker or a target for therapeutic intervention, clearly supporting the rejection's findings that the asserted utility is not substantial.

Beginning at p. 17 of the Brief, Appellants argue that, even is a *prima facie* case of lack of utility has been established, it should be withdrawn based on the totality of the evidence. Appellants again draw attention to the Ashkenazi declaration, urging that gene amplification even without polypeptide overexpression is useful in that it assists the clinician in tumor classification and selection of treatment modalities that are specific to the tumor, thus avoiding excess cost and side effects. This has been fully considered but is not found to be persuasive. The specification does not disclose such further testing of gene product overexpression. Therefore, the skilled artisan would have been

required to do the testing to reasonably confirm whether or not the PRO269 polypeptide is overexpressed. In view of such requirement, the products or services based on the claimed invention are not in "currently available" form for the public. Furthermore, the specification provides no assertion that the claimed PRO269 antibodies are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO269. For example, neither the specification nor the prior art discloses an agent that targets PRO269 that is useful for cancer therapy. This is also further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial.

At p. 18 of the Brief, Appellants argue that the opinion of Dr. Ashkenazi is supported by the Hanna and Mornin reference. Appellants urge that the publication evidences that the HER-2/neu gene is over-expressed in breast cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Appellants argue that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna and Mornin support the rejection, in that Hanna and Mornin show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments. Since the asserted utility for the claimed antibodies is not in currently available form, and requires further

experimentation to reasonably confirm the suggested use, the asserted utility is not substantial. Finally, it is no small matter to go from information regarding polypeptide expression levels in a tumor to designing a therapeutic regimen specific to the polypeptide expression profile. In Hanna and Mornin, Herceptin was discussed as a drug specific to tumors expressing HER-2/neu. Herceptin had been known prior to the publication of Hanna et al. No such drug is disclosed in the specification, nor in the prior art, regarding the PRO269 polypeptide. Identifying a drug specific for PRO269 would involve more than routine experimentation, as it would require a great amount of experimentation (e.g., screening agents for effects on PRO269 polypeptide and on tumor), considering there is no guidance or working examples relative to such drugs in the specification or the prior art.

At p. 18, Appellants urge that the examiner has misread Hanna and Mornin, and quote from Hanna and Mornin that, in general, FISH and IHC correlates well. Appellants urge that only a subset of tumors show discordant results. This has been fully considered but is not found to be persuasive. Hanna and Mornin do not appear to disclose the percentage of tumors having a correlation and those not having a correlation. However, Hanna and Mornin clearly caution the clinician not to assume that HER-2/neu polypeptide is overexpressed based on gene amplification tests, since administering Herceptin to patients not overexpressing HER-2/neu was harmful. Thus, the art directs the skilled artisan to do the further experimentation on the expression levels of the polypeptide.

At p. 18, last paragraph, Appellants argue that the specification demonstrates

PRO269 gene amplification in multiple lung tumors and concludes that PRO269 is a tumor associated gene like HER-2/neu. Appellants urge that gene amplification, in the majority of cases, influences mRNA and polypeptide levels, allegedly based on the art. Appellants conclude that the skilled artisan would reasonably expect that PRO269 polypeptide is overexpressed in lung tumors. This has been fully considered but is not found to be persuasive. PRO269 gene was not amplified in nine out of seventeen lung tumors tested. Therefore, screening a new lung tumor sample with a PRO269 probe would more likely than not provide a false negative result. Furthermore, the preponderance of the evidence clearly indicates that gene amplification cannot be assumed to correlate with polypeptide overexpression. See Pennica et al., Konopka et al., Hittelman, Sen, Godbout et al., Li et al., Hanna and Mornin, an even the Ashkenazi declaration and the Hyman et al. article. The art directs the skilled artisan to perform further experiments to determine whether or not a polypeptide is overexpressed in cancer tissue. Thus, since further experimentation is clearly required to reasonably confirm the asserted utility, the asserted utility is not substantial.

At the top of p. 19 of the Brief, Appellants argue that the examiner improperly views the further testing described in the Ashkenazi declaration as further characterization f the PRO269 polypeptide itself. Appellants assert that the experimentation described is only further characterization of the tumor, not the polypeptide. Appellants argue that the PRO269 polypeptide and its antibodies are useful in tumor categorization, enabling the physician to select a treatment modality that holds the most promise for successful treatment of a patient. This has been fully

considered but is not found to be persuasive. The tissue specific pattern of expression of a polypeptide is definitely a feature of the polypeptide itself. The determination of such is a form of characterizing the polypeptide. Furthermore, no treatment modalities specific to PRO269 have been disclosed in the specification or prior art. The identification of such would require significant further research, thus also indicating that the asserted utility is not substantial.

At p. 19 of the Brief, Appellants conclude by arguing that, based on the asserted utility for PRO269 in lung cancer diagnosis, the reduction to practice of the polypeptide of SEQ ID NO: 96, the disclosure of protocols for making chimeric PRO polypeptides and antibodies such as those claimed and for recombinant expression of PRO269, the disclosure of protocols for making PRO269 antibodies, and the gene amplification assay, the skilled artisan would know exactly how to make and use the claimed antibodies for diagnosis of lung cancers. Appellants urge that testing would have been routine and not undue. This has been fully considered but is not found to be persuasive. The rejection is supported by the preponderance of the totality of the evidence. Regarding the gene amplification assay itself, it is noted that the assay did not correct for aneuploidy, which is a common feature of non-cancerous, damaged lung epithelium (evidenced by Hittelman and Sen). The specification does not assert a utility for PRO269 as a biomarker for damaged, pre-cancerous tissue, and such is not a well-established utility. Gene amplification publications used matched tissue controls, unlike Appellants (Pennica et al., Godbout et al., Li et al.). Contrary to Appellants' assertions, the state of the art indicates that gene amplification is not generally associated with

overexpression of the encoded gene product, as evidenced by Sen, Pennica et al., Godbout et al., Hyman et al., and Li et al. The declaration setting forth the expert opinion of Dr. Ashkenazi contradicts the assertion of utility in the specification, wherein the specification indicates that gene amplification is associated with polypeptide overexpression but Dr. Ashkenazi indicates that this is not always the case. Hanna and Mornin provide evidence that the level of polypeptide expression must be tested empirically to determine whether or not the polypeptide can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the polypeptide level of PRO269 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since significant further research would have been required of the skilled artisan to reasonably confirm that PRO269 polypeptides are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents, the asserted utility is not substantial. Even more research would be required of the skilled artisan to determine if the PRO269 polypeptides or antibodies can be used as cancer therapeutics, since there is no evidence that PRO269 plays a role in cancer formation or progression such that inhibiting PRO269 would result in effective cancer therapy. In the absence of information regarding whether or not PRO269 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO269 **polypeptides and antibodies** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the

Art Unit: 1646

claimed antibodies. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

(12) Oral Hearing

It does not appear that Appellant has requested an oral hearing at this time. However, if an oral hearing is requested, the examiner requests the opportunity to present arguments at the hearing.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Elizabeth C. Kemmerer/

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